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Vasopressin receptor antagonists

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The first non-peptide vasopressin receptor antagonist (VRA) was recently approved by the United States Food and Drug Administration, and several others are now in late stages of clinical development. Phase 3 trials indicate that these agents predictably reduce urine osmolality, increase electrolyte-free water excretion, and raise serum sodium concentration. They are likely to become a mainstay of treatment of euvolemic and hypervolemic hyponatremia. Although tachyphylaxis to the hydro-osmotic effect of these agents does not appear to occur, their use is accompanied by an increase in thirst, and they do not always eliminate altogether the need for water restriction during treatment of hyponatremia. Experience with use of these agents for treatment of acute, severe, life-threatening hyponatremia as well as chronic hyponatremia is limited. Further studies are needed to determine how they are best used in these situations, but the risk of overly rapid correction of hyponatremia seems low. Results of long-term trials to determine the ability of VRAs to reduce morbidity or mortality in congestive heart failure or to slow the progression of polycystic kidney disease are awaited with great interest.

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The syndrome of inappropriate antidiuretic hormone secretion (SIADH), congestive heart failure (CHF), and cirrhosis are among many conditions associated with abnormal water retention mediated by arginine vasopressin (AVP) release inappropriate to plasma tonicity. Conventional therapies for euvolemic or hypervolemic hyponatremia, including water restriction, hypertonic saline, demeclocycline, and urea, all have significant drawbacks. Selective vasopressin receptor antagonists (VRAs) target the cause of abnormal water retention by producing an increase in electrolyte-free water excretion, or 'aquaresis', and could thus provide highly specific therapy. Early studies suggest that, in addition to their use as aquaretic agents, VRAs can potentially be used to treat nephrogenic diabetes insipidus (NDI) owing to AVP receptor mutations and may slow the progression of polycystic kidney disease. The first VRA was recently approved in the United States by the Food and Drug Administration (FDA) for clinical use in patients with euvolemic hyponatremia. This paper reviews the clinical experience to date with non-peptide VRAs and discusses their indications and potential future uses.

VASOPRESSIN RECEPTORS

AVP receptors are G-protein-coupled receptors. The three subtypes differ in localization and signal transduction mechanisms (Table 1). The vasopressin V1a receptor (V1aR) is a Gq-coupled receptor that activates phospholipase C and increases cytosolic free calcium. Its effect depends on its location. Vasopressin V2 receptors (V2R), which are found in vascular endothelium and the principal cells of the renal collecting and connecting tubules, effect release of von Willebrand factor and Factor 8 and mediate the hydro-osmotic effect of vasopressin. The V2R is a 41 kDa protein of 371 residues with seven transmembrane domains. Binding of AVP to the V2R activates the Gs adenylyl cyclase system, increasing intracellular levels of cyclic 3′,5′-adenosine monophosphate. The latter activates protein kinase A, which in turn phosphorylates preformed aquaporin-2 (AQP2) water channels localized in intracellular vesicles. Phosphorylation promotes trafficking to the apical membrane, followed by exocytic insertion of AQP2 vesicles into the cell membrane. This is the limiting step in rendering the collecting duct water permeable, as aquaporins 3 and 4 are constitutively present in the basolateral membrane, although AVP also regulates the former to some degree. AQP2 membrane insertion and

Table 1 | Vasopressin receptor location and functions

Receptor	Localization	Functions
V1a	Vascular smooth muscle	Vasoconstriction, myocardial hypertrophy
	Platelets	Platelet aggregation
	Hepatocytes	Glycogenolysis
	Myometrium	Uterine contraction
V1b[a]	Anterior pituitary	ACTH release
V2	Basolateral membrane collecting tubule	Insertion of AQP2 water channels into apical membrane, induction of AQP2 synthesis
	Vascular endothelium	vWF and factor 8 release
	Vascular smooth muscle	Vasodilatation

ACTH, adrenocorticotropin hormone; AQP2, aquaporin-2.
[a]Termed V3 in some classification schemes.

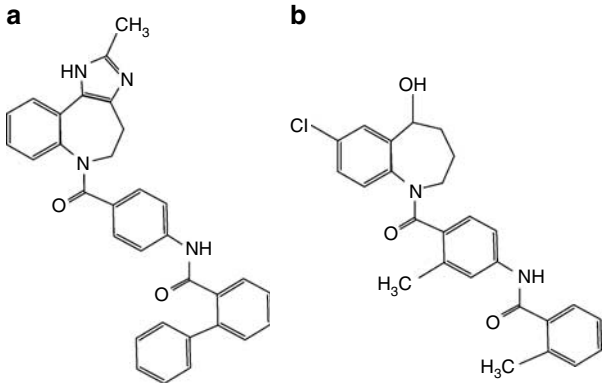

Figure 1 | Structure of the orally active VRAs. (**a**) Conivaptan, a combined V1a/V2 antagonist. (**b**) Tolvaptan, a selective V2 antagonist.

transcription are reduced when AVP is chronically suppressed, as in primary polydipsia. Diminished AVP effect, as seen with hypercalcemia, hypokalemia, lithium, and NDI, owing to V2R mutations, is also associated with reduced AQP2 expression.[1,2]

VASOPRESSIN RECEPTOR ANTAGONISTS

Initial development efforts on VRAs during the 1970s focused on peptide analogs derived from the selective V2R agonist desmopressin. In the late 1980s, it seemed likely that one such agent, a peptide with V2R antagonist effect in animals, would be successfully developed for use in humans. However, a phase 1 trial showed that the agent was a weak V2R agonist in humans, and further development of peptide antagonists was abandoned.[3] Also, the peptide antagonists had poor oral bioavailability, limiting their utility to parenteral administration. Using a functional screening strategy, non-peptide VRAs were subsequently identified. In 1993, Ohnishi *et al*[4] reported the first use of an orally active, non-peptide selective V2R antagonist to produce aquaresis in healthy men.

ROLE OF VASOPRESSIN IN HYPONATREMIC STATES

Normally, when osmolality falls below its set point, plasma AVP levels become undetectable, and an aquaresis results. In SIADH, AVP release is not fully suppressed, despite hypotonicity. In cirrhosis and CHF, impaired delivery of solute to the diluting sites or even a diminished glomerular filtration rate can impair maximal water-excretory capacity. However, the persistence of AVP release owing to non-osmotic stimuli is predominantly responsible for water retention in these disorders. Under ordinary circumstances, high-pressure baroreceptors in the ventricles, carotid sinuses, and aortic arch acting through vagal afferents tonically suppress release of AVP, renin, and catecholamines. Arterial under-distension and baroreceptor unloading in CHF inhibits this vagal tone. Consequently, AVP, catecholamine, renin, angiotensin, and aldosterone levels are elevated in patients with CHF.[5,6] In cirrhosis, splanchnic vasodilatation also leads to arterial underfilling with non-osmotic release of AVP. Patients with cirrhosis and ascites or edema can be classified according to whether they are able to excrete a standardized water load. Along with water retention, 'non-excretors' have worse liver disease, more sodium retention and ascites, and higher AVP, renin, and aldosterone levels than 'excretors' who handle a water load normally. Although glomerular filtration rate is lower in non-excretors than excretors, data from hypophysectomized animals with cirrhosis or from cirrhotic animals treated with demeclocycline show improved water excretion, and Brattleboro rats with cirrhosis do not have a water excretion defect. Taken together, these data suggest that non-osmotic release of AVP is principally responsible for the abnormal water retention of cirrhosis.[7] Thus, patients with hyponatremia caused by SIADH, CHF, and cirrhosis are all potential targets for treatment with VRAs.

ORALLY ACTIVE NON-PEPTIDE VRAs IN DEVELOPMENT

Four non-peptide agents, all benzazepine or oxindole derivatives, are now in various stages of clinical trials (Figure 1 and Table 2). Conivaptan is a combined V1aR and V2R antagonist; the others are selective V2R antagonists. In December 2005, conivaptan was approved by the US FDA for treatment of euvolemic hyponatremia. All agents of this class are inhibitors of the cytochrome *P*450 3A4 system, but conivaptan is the most potent. Although the drug is orally active, to minimize the possibility of drug interactions, the FDA has restricted its distribution to a parenteral form for short-term in-hospital use only. The other three VRAs have more limited CYP3A4 inhibitory activity and are being developed for long-term oral use.

Molecular modeling of binding sites suggests that these antagonists penetrate deeper into the transmembrane region of the V2R than native AVP. They thereby prevent binding of native hormone without themselves interacting with the H1 helix site that is critical for receptor-mediated G-protein activation (Figure 2).[8]

Table 2 | Non-peptide vasopressin antagonists currently under commercial development

Compound	Receptor	Route	Manufacturer
Conivaptan (YM-087)	V1a+V2	i.v.	Astellas (Tokyo, Japan)
Lixivaptan (VPA-985)	V2	Oral	CardioKine (Philadelphia, PA, USA)
Tolvaptan (OPC-41061)	V2	Oral	Otsuka (Tokyo, Japan)
SR-121463	V2	Oral	Sanofi-Aventis (Paris, France)

i.v., intravenous.

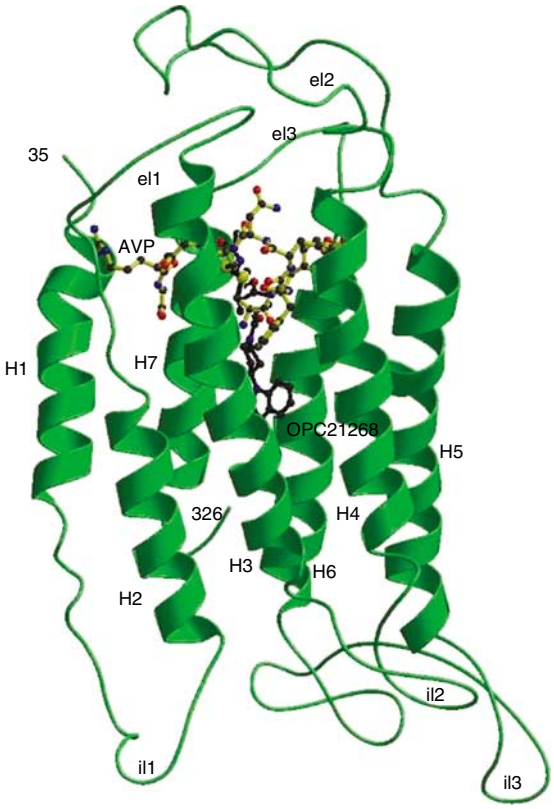

Figure 2 | V2 receptor shown as a ribbon diagram. For the receptor (green), loops labeled 'e' are extracellular and loops labeled 'i' are intracellular. Models of arginine vasopressin (AVP, multicolored) and a V2 receptor antagonist (OPC21268, dark blue) are shown at the sites where they would dock were the other not present. Binding sites are distinct with partial overlap. The antagonist, which lodges deeper in the receptor than AVP, prevents AVP docking but does not interact with the receptor's active site in the H1 helix. The figure was graciously provided by Dr Menachem Shoham and modified with permission from Macion-Dazard *et al.*[8]

Lixivaptan

As the greatest published experience is with lixivaptan, results using this agent will be discussed in detail. Based on preliminary reports, results with the other agents should be similar, although there are no published data to date in patients using SR121463B.

In a phase 2 trial, six individuals with SIADH and five individuals with cirrhosis received 50 or 100 mg lixivaptan or placebo twice daily. In the SIADH patients, serum sodium ($[Na^+]$) increased from 126 ± 5 to 133 ± 5.6 mmol/l after 48 h as urine flow rate increased from 0.84 ± 0.2 to 1.46 ± 0.4 ml/min and weight dropped by 1 kg. Urine osmolality fell from 414 ± 148 to 209 ± 55 mOsm/kg and urine sodium excretion fell from 82 ± 22 to 45 ± 21 mmol/24 h (all $P < 0.05$ compared with placebo). Plasma renin, aldosterone, and AVP levels and creatinine clearance were unchanged. Serum uric acid rose from 2.9 ± 0.8 to 3.7 ± 1.1 mg/dl and blood urea nitrogen from 11.7 ± 2.2 to 13.1 ± 1.9 mg/dl (both $P < 0.05$). The 7 mmol/l increase in $[Na^+]$ appeared to be due to the combination of water excretion (accounting for 5 mmol/l) and sodium retention (accounting for 1.5 mmol/l). The rise in blood urea nitrogen and uric acid along with the sodium retention were consistent with correction of water overexpansion via aquaresis. In the cirrhotic patients, $[Na^+]$ rose from 126 ± 2.9 to 133 ± 4.9 mmol/l over 72 h, uric acid was unchanged, and blood urea nitrogen fell slightly from 17.8 ± 4.5 to 14 ± 2.2 mg/dl. Urine sodium rose from 23 ± 18 to 65 ± 60 mmol/24 h. Potassium excretion also rose slightly. Plasma AVP levels rose from 1.9 ± 1.2 to 5.3 pg/ml (all $P < 0.05$), but renin and angiotensin levels did not change. Taken together, these changes indicate that correction of volume expansion in the SIADH patients was associated with sodium retention. In contrast, the increase in sodium and potassium excretion in the cirrhotic patients suggests that distal sodium delivery increased as the hyponatremia was corrected in these patients.[9]

In a dose-ranging trial, 27 patients with cirrhosis received single doses of placebo or 25– 300 mg of lixivaptan. Dose-related changes in urine flow rate, 1454 ± 858 versus 4568 ± 4385 ml/24 h; net fluid balance, 328 ± 811 versus -1608 ± 1570 ml/24 h; $[Na^+]$, 1.2 ± 1.0 versus 5.0 ± 3.0 mmol/l; minimum urine osmolality, 489 ± 235 versus 78 ± 29 mOsm/kg; and free water clearance, -0.36 ± 0.40 versus 6.76 ± 7.61 ml/min (all $P < 0.05$, placebo versus 300 mg) were observed along with a small but significant natriuresis.[10]

In a longer-term trial, 60 patients with cirrhosis received 50 or 100 mg lixivaptan or placebo twice daily, while maintaining a 1 l/d fluid restriction. After 7 days, $[Na^+]$ in the placebo-treated patients was unchanged but rose from 126.4 ± 4.4 to 132.3 ± 6.9 mmol/l in the 100 mg group. In the placebo, 50, and 100 mg groups, 0, 27, and 50% of patients normalized $[Na^+]$. For responders, mean time to complete response was 4.8 days in the 100 mg group and 5.7 days in the 50 mg group. Mean change in $[Na^+]$ per day was 0.1 ± 0.2, 0.8 ± 0.4, and 1.8 ± 0.5 mmol/l per 24 h in the placebo, 50, and 100 mg groups, respectively. A modest natriuresis also occurred.[11]

In a separate study, 44 patients with a $[Na^+]$ below 130 mmol/l were given lixivaptan (25, 125, or 250 mg b.i.d.) or placebo over 7 days, while maintained on a fluid restriction. The diverse study population comprised individuals with cirrhosis, CHF, and SIADH. The changes in $[Na^+]$ and urine osmolality over the course of the study are shown in Figure 3. The $[Na^+]$ rose in a dose-dependent fashion, but appeared to reach a plateau, in part because 12

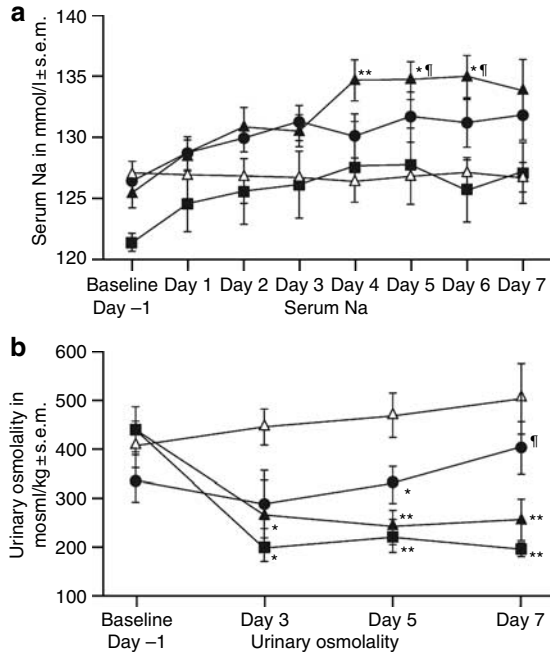

Figure 3 | Serum and urine response to lixivaptan. (**a**) Serum sodium and (**b**) urine osmolality during a 7-day course of placebo (Δ), or lixivaptan 25 mg b.i.d. (●), 125 mg b.i.d. (■), or 250 mg b.i.d. (▲). *$P<0.05$ versus placebo; **$P<0.01$ versus placebo; #$P<0.05$ versus 25 mg b.i.d.; ¶$P<0.05$ versus 125 mg b.i.d. Reproduced with permission from Wong *et al.*[12]

of 44 subjects dropped out (half because of postural hypotension) and in part because of the complex rules that called for withholding medication and liberalizing fluid intake if the $[Na^+]$ increased more than 8 mmol/l from the previous measurement or if the $[Na^+]$ rose above 142 mmol/l. More patients in the higher dosage groups required medication holds, including half the patients in the highest dosage group. Free water clearance was higher and urine osmolality lower than placebo in the two higher dosage groups, but again the results were blunted because of medication stop rules. As measured by visual analog scale, thirst increased in all groups receiving active medication, but reached statistical significance versus baseline or placebo only in the highest dosage group. Plasma AVP levels on the final day of the study were higher than placebo in the two highest dosage groups only; separate data were not provided for SIADH and cirrhosis patients. Plasma norepinephrine, renin, and aldosterone levels were unchanged. This study makes it clear that care will be needed in selecting the long-term dose of a VRA if excessive aquaresis is to be avoided.[12]

Tolvaptan

The original non-peptide V2R antagonist, OPC-31260, demonstrated the anticipated effect on urinary concentration and water excretion in studies in normal individuals and patients with cirrhosis or SIADH.[4,13–15] Subsequent commercial development by Otsuka has focused on the more potent compound OPC-41061, tolvaptan, which has been studied primarily in individuals with CHF. In one study, 254 patients with NYHA class 2 or 3 CHF were maintained on stable doses of furosemide and randomized to receive tolvaptan 30, 45, or 60 mg or placebo once daily for 25 days. Patients were not fluid restricted. After 24 h, the tolvaptan patients lost 0.8 kg, and the placebo patients gained 0.32 kg. This difference was significant, similar in all dosage groups, and persisted with no additional weight loss over the study period. Urine osmolality at study conclusion was 52.05 ± 144.96 mOsm/kg below baseline in the tolvaptan 60 mg group ($P<0.05$) and 163.7 ± 202.53 mOsm/kg above baseline in the placebo group (NS). The 24-h sodium excretion in the first day was approximately 50% higher in the treated groups (e.g., 355 mmol/24 for the tolvaptan 60 mg group, 193.7 mmol/l for the placebo group, $P<0.05$). In the tolvaptan group, the $[Na^+]$ increased approximately 3 mmol/l on day 1, but was unchanged in the placebo group. In the initially normonatremic tolvaptan patients, the $[Na^+]$ returned to baseline by the end of the study. Among the 28% of enrollees who were hyponatremic at study initiation, there was a greater increase, and $[Na^+]$ concentrations remained within the normal range through study termination in twice as many initially hyponatremic tolvaptan-treated individuals (82%) compared to placebo. Hypernatremia developed in 5, 6, 11, and 13% of subjects in the placebo, 30, 45, and 60 mg groups, respectively. Relative to the placebo group, edema scores improved, thirst increased, and vasopressin levels trended upward in the active treatment group. Requisite balance data were not obtained, but it is reasonable to assume that $[Na^+]$ levels drifted back to baseline despite lower urine osmolalities because water intake increased in the treatment groups. In summary, tolvaptan had a modest effect on weight and led to a correction of hyponatremia that was sustained for 25 days without significant hypernatremia.[16]

In a companion study, 319 patients with ejection fraction $<40\%$, who required hospitalization for a CHF exacerbation, were randomized to receive placebo or 30, 60, or 90 mg tolvaptan. The primary end point was in-hospital weight loss, which was greater in the tolvaptan group. The weight change, pattern of $[Na^+]$ change, and rate of normalization of $[Na^+]$ in hyponatremic patients in this study were similar to those in the previous study. Additional primary end points were worsening CHF or unscheduled visits for CHF within 60 days. Although these were not different among the treatment groups, in *post-hoc* analysis, 60-day mortality was significantly lower in tolvaptan-treated patients with renal dysfunction or severe congestion at baseline.[17] This study was not powered to determine whether tolvaptan might reduce cardiovascular mortality. However, a large-scale, multicenter phase 3 trial comparing tolvaptan 30 mg daily to placebo is currently underway to answer this important question.[18]

In a more recent trial with tolvaptan, SALT2 (sodium assessment with increasing levels of tolvaptan in hyponatremia), approximately 200 hyponatremic patients received 15–60 mg tolvaptan in a stepwise fashion for 30 days. Similar to the lixivaptan trials, significantly greater increases in serum

[Na^+] occurred in the tolvaptan-treated patients compared to placebo, although 25% of the patients dropped out, and resistance (defined as a failure of [Na^+] to rise by 5 mmol/l) occurred in 37% of cirrhosis, 17% of CHF, and 11% of SIADH patients (Gross P, presented at the American Society of Nephrology Annual Meeting, Philadelphia, November 2005).

Conivaptan

Conivaptan is a mixed V1aR and V2R antagonist. Use of a combined antagonist has the theoretical advantage of mitigating any unopposed V1aR activation, which could be particularly desirable in patients with CHF. In a study of 142 patients with NYHA class 3 or 4 CHF who were randomized to receive placebo or a single intravenous dose of conivaptan, 10, 20, or 40 mg, active drug at the 40 mg dose reduced pulmonary capillary wedge pressure by 4.6 ± 0.7 mm Hg compared with 2.6 ± 0.7 mm Hg for placebo ($P < 0.05$). Right atrial pressure was also significantly lower in the treatment groups. These effects were sustained for 12 h after drug dosing. Urine osmolality fell and urine output rose in the treatment groups, but cardiac index, mean arterial pressure, systemic vascular resistance, pulmonary vascular resistance, and heart rate were not significantly different. [Na^+] did not change significantly, although a 1.5 mmol/l rise was observed in the 40 mg group along with a small and significant rise in AVP level.[19] Whether the prompt reduction in pulmonary capillary wedge pressure was entirely due to the V2R-mediated aquaresis or also involved vasorelaxation owing to V1aR antagonism cannot be ascertained.

Results of a phase 3 clinical trial in patients with SIADH or CHF and hyponatremia randomized to receive placebo or a 20 mg bolus of conivaptan followed by continuous intravenous infusion of 40 or 80 mg conivaptan per day for 4 days along with modest water restriction showed a mean increase in [Na^+] of 2.0 ± 0.8 mmol/l in the placebo group, 6.8 ± 0.8 mmol/l in the 40 mg, and 9.0 ± 0.8 mmol/l in the 80 mg group ($P < 0.05$ for both versus placebo). Of note was the more rapid correction of [Na^+] in the first 24 h than has been reported to date with the oral V2R antagonists, perhaps reflecting enhanced bioavailability of the intravenous preparation; median time to a 4 mmol/l increase in [Na^+] was 23.7 h in the 40 mg group and 23.4 h in the 80 mg group. [Na^+] increased by 6 mmol/l or more in 20.7, 69, and 88.5% of individuals in the three groups, respectively. Overly rapid correction was rarely observed and was not associated with clinical consequences. The only potentially concerning side effect was local irritation at the infusion site (Verbalis JG *et al. J Am Soc Nephrol* 2004; 15: 356A). Oral dosing produced similar changes in [Na^+] (Verbalis JG *et al. Endocrine Society 87th Annual Meeting*, San Diego, 2004 (abstract P3–P183)).

Conivaptan, 20 mg orally twice daily, along with 1.5 l fluid restriction was used successfully to maintain a normal [Na^+] in two patients with chronic hyponatremia owing to SIADH. Fluid restriction alone was unsuccessful, but [Na^+] was maintained within the normal range during the 90-day period of combined therapy (Figure 4).[20] Although effective, the oral preparation is no longer being developed for clinical use because of concerns during long-term use about interactions with other drugs metabolized by the CYP3A4 pathway.

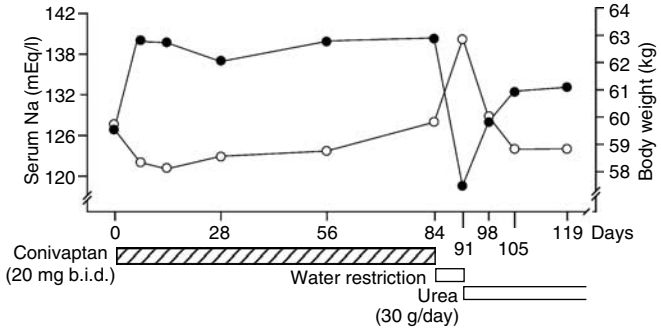

Figure 4 | Changes in body weight (○) and serum sodium levels (●) during treatment of a patient with SIADH with conivaptan, water restriction, or urea. Reproduced with permission from Decaux.[20]

POTENTIAL USES FOR V2R OR COMBINED V1aR + V2R ANTAGONISTS

Hyponatremia

V2R antagonists will become a mainstay of treatment for euvolemic (i.e., SIADH, postoperative hyponatremia) and hypervolemic hyponatremia (i.e., CHF and cirrhosis). As detailed above, these agents predictably cause an aquaresis leading to increased [Na^+] in the majority of patients with hyponatremia due to SIADH, CHF, and cirrhosis. Although the initial FDA approval for conivaptan was only for the indication of euvolemic hyponatremia, increased exposure of larger numbers of patients with CHF to VRAs should eventually lead to approval for the indication of hypervolemic hyponatremia. The optimum use of VRAs has not yet been determined, but some predictions can be made with reasonable certainty. For hyponatremia in hospitalized patients, who are unable to take medication orally or for those in whom a more rapid correction of hyponatremia is desired, conivaptan will likely be the preferred agent. Phase 3 studies show that it reliably raises [Na^+] over the short term beginning as early as 1–2 h after administration, and permits normalization of [Na^+] in most hyponatremic patients over a 4-day course of treatment (Verbalis JG *et al. J Am Soc Nephrol* 2004; 15: 356A; Verbalis JG *et al. Endocrine Society 87th Annual Meeting*, San Diego, 2004, Abstract P3–P183). Selective V2R antagonists such as lixivaptan, tolvaptan, or SR121463B will likely be useful in patients for whom oral therapy is suitable and for more chronic forms of hyponatremia.

Despite the attractiveness of using a pure aquaretic agent to correct life-threatening hyponatremia, insufficient data are available from clinical trials to know if sufficiently rapid correction can be achieved in patients with acute, severe hyponatremia without the use of hypertonic saline. Theoretically, both could be used initially; the hypertonic saline

could be stopped after the $[Na^+]$ increases a few mmol/l, with the remainder of the first day correction to be accomplished with the water diuresis. The two agents may be complementary in that the hypertonic saline infusion would cause sufficient expansion to mitigate any volume depletion resulting from the aquaresis.

Most studies employing these agents to treat hyponatremia have been of limited duration, generally only 1–7 days. However, sufficient data from longer-term studies exist to expect that the agents will likely prove to be highly useful in chronic hyponatremia, owing to SIADH, cirrhosis, and CHF. Although the effect of VRAs on plasma AVP levels is variable, it bears emphasis that the VRAs often increase thirst even in hyponatremic patients and, unless restricted, water intake generally increases as well. As an example of this, in the initial tolvaptan CHF study, the $[Na^+]$ rose only during the first day, despite a persistently dilute urine.[16] Thus, use of VRAs will mitigate, but in many cases not altogether eliminate the need for fluid restriction.[12,20]

Safety issues must also be considered carefully with any new class of agents. The possibility of overcorrection has been of significant concern in all of the VRA clinical trials, but to date osmotic demyelination has not been reported with any agent. Nonetheless, it is anticipated that the agents will need to be used judiciously if correction of the $[Na^+]$ at a rate faster than 8–12 mmol/l/24 h is to be avoided.[21] Because of their <12 h half-life, all of the agents will require daily or continuous dosing to maintain activity, so it will be possible to limit the $[Na^+]$ rise by stopping the drug or reducing the dosage. If necessary, hypotonic fluid can be infused to abrogate the rise in $[Na^+]$ until the aquaresis abates. These safeguards should be sufficient to protect against overly rapid correction if $[Na^+]$ levels are monitored frequently during the course of active treatment. A second major concern is to avoid using VRAs in cases of hypovolemic hyponatremia, where an aquaresis would aggravate the underlying volume contraction and potentially cause hypotension. This can be avoided by careful attention to the appropriate differential diagnosis among the different subtypes of hyponatremia.[22] A third concern is the production of hypotension, particularly with antagonists having activity at V1aR. This has not been reported as a significant adverse event in the conivaptan clinical trials to date, but, because of the potential for splanchnic vasodilatation that could produce hypotension or promote variceal bleeding, effects of conivaptan have not been carefully examined in patients with cirrhosis. The potential for serious drug interactions via interference with CYP3A4 metabolism of other drugs must be recognized. This will likely not be of concern with short-term use of VRAs such as conivaptan, but may cause problems during long-term therapy, requiring appropriate monitoring. Finally, whether there will be any adverse effect of V2R inhibition in vascular endothelium is unknown. Bleeding complications have not been reported to date, but surveillance will be needed now that a V2R antagonist will soon be in general use.

Congestive heart failure

It is well established that the neurohormonal activation characteristic of CHF, including increased renin, angiotensin, aldosterone, and catecholamines, contributes to progression of CHF.[23] Abundant evidence from large-scale clinical trials attests to the reduction in cardiovascular mortality that accrues from treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-adrenergic blockers, and aldosterone antagonists.[24] Subgroup analysis suggests that cardiovascular mortality may be reduced by the selective V2R antagonist tolvaptan in the higher risk group with kidney function impairment or severe congestive findings.[17] As the V1aR is responsible for the pressor and mitogenic effects of AVP and as plasma AVP levels rise in some settings during V2R blockade, it is also possible that long-term isolated V2R blockade could prove deleterious to patients with CHF. A well-powered study to determine whether selective V2R antagonist therapy will prove as beneficial as other inhibitors of the CHF neurohormonal cascade is ongoing,[18] although it will not establish whether long-term combined V1a and V2R antagonism might be superior. Until such studies have been completed and an FDA indication is granted for use in CHF with or without accompanying hyponatremia, VRAs are not recommended in patients with CHF.

Cirrhosis

Although the hyponatremia of cirrhosis is analogous to that of CHF in many respects, the presence of portal hypertension in these patients presents additional concerns, namely, that V1aR blockade may produce hypotension and variceal bleeding owing to antagonism of AVP pressor effects in this vascular bed. Consequently, at the present time, only selective V2R antagonists can be recommended for these patients. The lixivaptan and tolvaptan trials provide conflicting data as to whether cirrhotic patients will be as responsive as patients with other causes of hyponatremia.

Polycystic kidney disease

Cyclic 3′,5′-adenosine monophosphate-dependent genes promote fluid secretion into developing renal cysts and increase cell proliferation.[25] Polycystin-1 may directly inhibit adenyl cyclase, and polycystin-2 acts to increase intracellular calcium, which in turn inhibits adenyl cyclase and increases the activity of collecting duct phosphodiesterases. Thus, polycystin defects may promote cyst development because they lead to increases in intracellular cyclic 3′,5′-adenosine monophosphate.[26] The second messenger for AVP acting at the V2R is cyclic 3′,5′-adenosine monophosphate. Studies in several animal models of polycystic kidney disease have shown a reduction in kidney size and cyst volume after treatment with the V2R antagonist OPC-31260.[26] A phase 2 dose-ranging and tolerability trial of tolvaptan in patients with autosomal dominant polycystic kidney disease is now ongoing, and the results of a full-scale therapeutic trial would be of great interest (Chapman A *et al. J Am Soc Nephrol* 2005; 16: 68A).

Nephrogenic diabetes insipidus

Congenital NDI may result from V2R or AQP2 mutations. The V2R mutations include type 1 mutations that prevent AVP binding, type 2 mutations that cause misfolding and interfere with trafficking of receptor from endoplasmic reticulum to cell membrane, and type 3 mutations that lead to transcription of unstable mRNA. Exogenously administered V2R antagonists can bind to misfolded intracellular V2R, and improve transport of V2R to the cell membrane.[27] Clinical studies in patients with X-linked NDI showed that the selective V1aR antagonist relcovaptan (SR49059, Sanofi-Aventis) significantly increased urine osmolality (98 ± 22–170 ± 52 mOsm/kg) and decreased 24-h urine flow (11.9 ± 2.3–8.2 ± 2.0 l).[28] Although the effect was modest, these results suggest that V1aR and/or V2R antagonists might serve as molecular chaperones to mitigate misfolding defects in selected patients with type 2 NDI.

CONCLUSIONS

Specific VRAs for clinical use have been long awaited. The recent FDA approval of conivaptan ushers in a new era in the treatment of hyponatremia. Use in patients with euvolemic hyponatremia is now permitted; additional clinical data to confirm safety of VRAs in CHF and cirrhosis should soon allow their use in hypervolemic hyponatremia. Most studies in hyponatremic patients to date have only been short term. Hence, the most appropriate way to use these agents, their long-term response rates, how important the role of water restriction will remain during chronic use, and whether correction of chronic hyponatremia will result in improved cognitive function, quality of life, or functional status remain important unknowns. Similarly, whether the effect of VRAs will be predictable enough to make them useful in acute, symptomatic hyponatremia also remains uncertain. VRAs may prove to be beneficial as well for effects that are not directly related to correction of hypotonicity. These include potential roles to enhance the cocktail of neurohumoral blockade employed to reduce mortality in CHF, to slow the progression of cyst growth in polycystic kidney disease, and to ameliorate polyuria in some forms of congenital NDI. All of these as well as presently unrecognized uses will await the results from both large-scale outcome trials and focused small-scale trials with VRAs.

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